Effect of ulinastatin + thymosin adjuvant therapy on inflammatory and stress response in patients with severe pneumonia

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ABSTRACT

Objective: To investigate the effect of ulinastatin + thymosin adjuvant therapy on inflammatory and stress response in patients with severe pneumonia. Methods: A total of 66 patients with severe pneumonia who were diagnosed and treated in Huanggang Central Hospital between July 2016 and July 2017 were divided into control group (n=33) and study group (n=33) by random number table. Control group received routine therapy for severe pneumonia, and study group received routine therapy combined with ulinastatin + thymosin adjuvant therapy, which lasted for 1 week. The differences in serum levels of inflammatory factors and stress hormones were compared between the two groups before and after treatment. Results: Before treatment, the differences in serum levels of inflammatory factors and stress hormones were not statistically significant between the two groups. After 1 week of treatment, serum levels of inflammatory factors and stress hormones of both groups of patients were lower than those before treatment, serum levels of pro-inflammatory factors IL-1β, IL-2, IL-6, IL-8 and TNF-α as well as anti-inflammatory factors IL-4, IL-10 and IL-13 of study group were lower than those of control group, and serum stress hormones Ang I, Ang II, NE and Cor levels were lower than those of control group. Conclusion: Routine therapy combined with ulinastatin + thymosin adjuvant therapy can further inhibit the systemic inflammatory response and stress response and optimize the overall condition in patients with severe pneumonia.

1. Introduction

Severe pneumonia is the serious disease after common pneumonia progresses and involves multiple organs, patients can develop circulatory disturbance and even shock, and be accompanied by dysfunction of important organs such as heart and kidney, and they may die in a short time if not rescued in time[1,2]. Anti-infection, anti-shock, respiratory support, nutrition support and so on are the routine therapies for patients with severe pneumonia, they can inhibit pathogenic toxicity and improve the patients' clinical symptoms to a certain extent, but there is still persistent systemic inflammatory stress response in some patients, and other drugs are needed to expand the curative effect and stabilize the disease. Ulinastatin has been successfully applied in a variety of systemic infectious diseases, which has multiple effects such as inhibiting proteolytic enzyme activity, inhibiting inflammatory mediator release and scavenging oxygen free radicals[3,4]; thymosin is a cellular immunomodulator, which has the important functions such as enhancing cellular immunity and regulating the immune balance of the body. In this research, ulinastatin and thymosin were used as adjuvant drugs for the treatment of patients with severe pneumonia, and their application value was discussed from inflammatory response and stress response, specifically reported as follows.

2. Information and methods

2.1 Case information

A total of 66 patients with severe pneumonia were diagnosed and treated in the hospital between July 2016 and July 2017. The random number table method was used to divide them into control group and study group, 33 cases in each group. Control group included 18 males and 15 females that were 31-78 years old; there
were 17 males and 16 females in the study group, and they were 34-79 years old. The baseline data of the two groups were comparable and the follow-up study plan was approved by the ethics committee of the hospital.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) in line with the diagnostic criteria for clinical severe pneumonia; (2) without history of pneumonia within 6 months prior to admission; (3) families of the patients signed the informed consent; (4) no cases had been lost in the midway.

Exclusion criteria: (1) combined with chronic bronchitis, asthma, COPD and other basic pulmonary diseases; (2) allergic to ulinastatin and thymosin; (3) combined with the systemic infectious symptoms caused by other diseases; (4) combined with hyperthyroidism, pheochromocytoma and other diseases that could lead to systemic stress; (5) combined with malignant tumor diseases.

2.3 Therapy

Control group received clinical routine therapy for severe pneumonia, including oxygen uptake, anti-infection, fluid infusion, phlegm reducing, electrolyte and acid-base imbalance correcting, nutritional support, etc.

On the basis of above routine treatment, observation group received adjuvant ulinastatin + thymosin therapy, specifically as follows: ulinastatin 300 000 units in 100 mL saline, by slow intravenous drip (finished within 1 h), 2 times/d; thymosin 1.6 mg, by subcutaneous injection, 2 times/d, both for 1 week in a row.

2.4 Observation indexes

Before treatment and after 1 week of treatment, cubital venous blood samples were extracted from two groups of patients at 8:00 a.m. and placed in heparinized sterile EP tubes to separate blood samples were extracted from two groups of patients at 8:00 a.m. and placed in heparinized sterile EP tubes to separate

2.5 Statistical methods

Inflammatory factors and stress hormones were input in software SPSS 26.0, t test was used to calculate statistics $P$ and the differences were significant statistically if $P<0.05$.

3. Results

3.1 Inflammatory factors

Comparison of serum levels of pro-inflammatory factors IL-1 $\beta$, IL-2, IL-6, IL-8 and TNF- $\alpha$ as well as anti-inflammatory factors IL-4, IL-10 and IL-13 between two groups of patients before and after treatment was as follows: before treatment, serum levels of pro-inflammatory factors IL-1 $\beta$, IL-2, IL-6, IL-8 and TNF- $\alpha$ as well as anti-inflammatory factors IL-4, IL-10 and IL-13 were not significantly different between the two groups ($P>0.05$). After 1 week of treatment, serum levels of pro-inflammatory factors IL-1 $\beta$, IL-2, IL-6, IL-8 and TNF- $\alpha$ as well as anti-inflammatory factors IL-4, IL-10 and IL-13 of both groups of patients were lower than those before treatment; serum levels of pro-inflammatory factors IL-1 $\beta$, IL-2, IL-6, IL-8 and TNF- $\alpha$ as well as anti-inflammatory factors IL-4, IL-10 and IL-13 of study group were lower than those of control group ($P<0.05$), shown in Table 1 and 2.

3.2 Stress hormones

Comparison of serum levels of stress hormones Ang I (pg/mL), Ang II (pg/mL), NE (ng/mL) and Cor (ng/mL) between two groups of patients before and after treatment was as follows: before treatment, serum Ang I, Ang II, NE and Cor levels were not

### Table 1

Comparison of serum pro-inflammatory factor levels (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>$n$</th>
<th>Time</th>
<th>IL-1 $\beta$</th>
<th>IL-2</th>
<th>IL-6</th>
<th>IL-8</th>
<th>TNF- $\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33</td>
<td>Before treatment</td>
<td>74.28±8.11</td>
<td>15.38±1.07</td>
<td>45.95±6.12</td>
<td>50.82±5.91</td>
<td>92.37±10.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 week of treatment</td>
<td>60.12±6.42</td>
<td>11.52±1.69*</td>
<td>32.74±4.09*</td>
<td>32.19±4.52</td>
<td>70.61±6.84*</td>
</tr>
<tr>
<td>Study</td>
<td>33</td>
<td>Before treatment</td>
<td>75.07±8.35</td>
<td>15.41±1.98</td>
<td>45.83±6.67</td>
<td>50.63±5.47</td>
<td>92.58±9.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 week of treatment</td>
<td>40.38±4.91</td>
<td>7.37±0.86*</td>
<td>17.63±2.48*</td>
<td>15.38±1.79*</td>
<td>37.20±4.52</td>
</tr>
</tbody>
</table>

### Table 2

Comparison of serum anti-inflammatory factor levels (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>$n$</th>
<th>Time</th>
<th>IL-4</th>
<th>IL-10</th>
<th>IL-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33</td>
<td>Before treatment</td>
<td>24.48±2.71</td>
<td>51.28±5.49</td>
<td>31.59±4.25</td>
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<td></td>
<td></td>
<td>After 1 week of treatment</td>
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<td>31.07±3.66</td>
<td>22.66±2.78</td>
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<tr>
<td>Study</td>
<td>33</td>
<td>Before treatment</td>
<td>24.39±2.62</td>
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<td>13.29±1.61</td>
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</tbody>
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Note: compared with same group before treatment. $^{*}P<0.05$. 

**Comparison of serum anti-inflammatory factor levels (pg/mL).**

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**Comparison of serum anti-inflammatory factor levels (pg/mL).**

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</tbody>
</table>

Note: compared with same group before treatment. $^{*}P<0.05$. 

**Comparison of serum anti-inflammatory factor levels (pg/mL).**
Ang groups of patients were lower than those before treatment; serum immune function
immunomodulator, which can cause the stem cells produced by
those of control group (inflammatory response syndrome (SIRS) and multiple organ
various clinical symptoms and avoid disease progression to systemic
necessary to actively control the pathogenic bacteria, optimize the
4. Discussion
Note: compared with same group before treatment,
Comparison of serum stress hormone levels. Table 3.
<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Ang I</th>
<th>Ang II</th>
<th>NE</th>
<th>Cor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>33</td>
<td>Before treatment</td>
<td>74.28±8.11</td>
<td>49.27±5.61</td>
<td>60.71±6.58</td>
<td>298.37±34.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 week</td>
<td>56.19±6.43*</td>
<td>38.91±4.52*</td>
<td>45.88±6.21*</td>
<td>173.49±21.53*</td>
</tr>
<tr>
<td>Study group</td>
<td>33</td>
<td>Before treatment</td>
<td>74.34±8.09</td>
<td>49.32±5.48</td>
<td>60.49±6.37</td>
<td>297.69±33.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 week</td>
<td>38.41±4.52*</td>
<td>27.45±3.29*</td>
<td>27.31±3.42*</td>
<td>90.74±9.81*</td>
</tr>
</tbody>
</table>

There are significantly different between the two groups (P>0.05). After 1
week of treatment, serum Ang I, Ang II, NE and Cor levels of both
groups of patients were lower than those before treatment; serum
Ang I, Ang II, NE and Cor levels of study group were lower than
those of control group (P<0.05), shown in Table 3.

4. Discussion
Severe pneumonia is critical and progresses rapidly, and it is
necessary to actively control the pathogenic bacteria, optimize the
various clinical symptoms and avoid disease progression to systemic
inflammatory response syndrome (SIRS) and multiple organ
function disorder syndrome (MODS)[5,6]. Anti-infection, anti-shock,
respiratory support, etc as the routine therapies, they can alleviate
the illness to a certain extent, but the weak autoimmunity, strong
pathogenic toxicity and other factors in some patients can cause
disease progression and even death of patients in a short time[7,8].
How to optimize the treatment outcome of patients with severe
pneumonia is a profound subject, and it may be a feasible method to
add targeted drugs that resist inflammation and strengthen the body’s resistance. Ulinastatin is a glycoprotein extracted from fresh urine,
which belongs to protease inhibitor, has been successfully applied in the
treatment of acute pancreatitis, acute onset of chronic pancreatitis
and so on, has been proven to be able to optimize the prognosis of
patients with cardiac surgery, has multiple effects such as stabilizing
lysosomal enzyme, inhibiting the release of inflammatory mediators
and remove oxygen free radicals[9,10]. Thymosin belongs to cellular
immunomodulator, which can cause the stem cells produced by
bone marrow to turn to mature T cells and enhance the mature T cell response to antigenic stimulation to finally enhance the cellular
immune function[11,12]. In this research, ulinastatin and thymosin were
used as auxiliary medicines for the treatment of patients with severe pneumonia, and the influence of the therapy on patients’
systemic state was discussed in order to provide reference for subsequent therapy establishment for similar patients.

There is severe systemic inflammatory response in patients with
severe pneumonia. After pathogen infects pulmonary bronchi, the
mononuclear macrophages and neutrophils further accumulate
and release a large amount of pro-inflammatory mediators, which can enter into the blood circulation through intrapulmonary blood
vessels and cause systemic inflammatory response. When the
pathogenic bacteria continuously secrete toxins and induce the
synthesis of inflammatory mediators, the inflammatory response
continues to worsen and even lead to the presence of SIRS[13,14].
The contents of inflammatory factors in circulating blood of patients with severe pneumonia can objectively reflect the disease
severity of and evaluate the effectiveness of the clinical treatment
strategy. IL-1β, IL-2, IL-6, IL-8 and TNF-α are all typical pro-
inflammatory factors, they are released into the blood early after
the pathogen infection, and their levels increase slightly in patients
with common pneumonia, and can only increase significantly when severe infection occurs[15,16]. In physiological state, the levels of pro-inflammatory and anti-inflammatory factors are in dynamic
equilibrium, the contents of above pro-inflammatory factors increase
early after infection, and the contents of IL-4, IL-10, IL-13 and other
anti-inflammatory factors also increase accordingly to neutralize
the pro-inflammatory factors and inhibit the inflammatory response
from expanding; when the inflammatory response is under control
and the pro-inflammatory factor secretion decreases, the synthesis of
anti-inflammatory factors decreases accordingly, so the fluctuation
trend of serum contents of these two is consistent as a whole[17,18].
In this study, the changes in serum levels of above inflammatory
cytokines were compared between the two groups of patients, and
it was found that compared with those before treatment, serum
levels of pro-inflammatory factors IL-1β, IL-2, IL-6, IL-8 and
TNF-α as well as anti-inflammatory factors IL-4, IL-10 and IL-13 of both groups decreased after treatment; further compared with
those of control group, serum levels of pro-inflammatory factors
IL-1β, IL-2, IL-6, IL-8 and TNF-α as well as anti-inflammatory
factors IL-4, IL-10 and IL-13 of study group were lower after
treatment, indicating that ulinastatin + thymosin adjuvant therapy based on routine therapy can more effectively inhibit the systemic
inflammatory response in patients with severe pneumonia.

The systemic inflammatory response caused by pathogenic bacteria
can directly induce stress response, accelerate protein decomposition and inhibit the immune function so as to increase the difficulty
in disease control[19,20]. Many studies have confirmed that the
expression levels of stress hormones such as Ang I, Ang II, NE
and Cor increase in patients with severe pneumonia, and the specific
levels are consistent with the illness severity and can reflect the
feasibility and effectiveness of clinical treatment[21,22]. The study
results showed that compared with those before treatment, serum stress hormones such as Ang I, Ang II, NE and Cor levels of both groups decreased after treatment; further compared with those of control group, serum Ang I, Ang II, NE and Cor contents of study group were lower after treatment, confirming that ulinastatin + thymosin adjuvant therapy can effectively inhibit the systemic stress response in patients with severe pneumonia, which is on the one hand, related to its effect on inhibiting inflammatory response, and on the other hand, associated with the thymosin effect on enhancing the cellular immune function.

Thus, it is concluded that in addition to routine therapy, ulinastatin + thymosin adjuvant therapy can further inhibit the systemic inflammatory response and stress response and optimize the overall condition of patients with severe pneumonia, and it is worthy of popularization and application in clinical practice in the future.

References


